The prior amendments by the Applicants did not require the new ground of rejection, the amendments merely combined limitations already existing in claims 1-3, or else merely clarified the intent of the terms used in the claims for the purpose of 35 U.S.C. 112. None of claims 1-3 were previously rejected based upon a combination of three references.

The present rejection of claim 1 is therefore a new ground of rejection improperly made final. ***The final rejection should therefore be withdrawn!***

Arntzen et al. teaches a method for making a transgenic tobacco, tomato or potato that expresses HBsAg.

Notwithstanding the Examiner's assertion, **Arntzen et al. does not teach "methods of making a transgenic plant expressing an immunogen derived from hepatitis B surface antigen, wherein the immunogen is capable of eliciting an immune response in an animal by consumption of the plant material."**

Arntzen et al. pays lip service to raising an immune response by ingestion, but in fact give no examples or teachings for obtaining such a result. **The only actual plant examples in Arntzen et al. relate to tomatoes and tobacco. There is no example of ingestion of either one and certainly no example showing that ingestion of either raises an immune response.** In fact, ingestion of the transgenic tomato does not raise any significant immune response (see the enclosed Rule 132 Declaration of Dr. Yasmin Thanavala) and certainly tobacco cannot be used for such a purpose because it is toxic. **Since there is no teaching in Arntzen et al. of how oral immunization to HBsAg**

might be accomplished using a transgenic plant, and in fact the plants made in the examples do not function orally to raise an immune response, as Arntzen et al. alleges, it is clear that there is insufficient teaching or suggestion in Arntzen et al. to support a rejection of the present claims whether the reference is considered alone or in combination with the other cited references.

Simply making an unsupported allegation in a reference without a teaching as to how the allegation might be accomplished, is not a sufficient teaching to make a method for accomplishing the desired result obvious to one skilled in the art. Prophetic statements cannot be used to form the basis of a rejection, especially when they are unsupported and not true.

Arntzen et al. itself teaches and recognize that not all antigens would cause an immune response if ingested.

Arntzen et al. says in column 15 beginning at line 27,

"The vaccines are conventionally administered parenterally, by injection, for example either subcutaneously or intramuscularly. Additional formulations which are suitable for other modes of administration include suppositories and, ***in some cases***, oral formulations or aerosols." (emphasis added).

But there is no teaching or suggestion in Arntzen et al. of how the "some cases" could be determined or how the "some cases" could be accomplished.

While Arntzen et al. suggest that tomato juice containing HBsAg might be used as a vaccine, in fact Arntzen provides no supporting data showing any immune response whatsoever to tomato juice or any other plant containing HBsAg. To the extent that Arntzen teaches that tomato juice or any other plant material containing HBsAg can be

used as a vaccine, it is an inoperative reference since there is no teaching or suggestion as to how that might be done. ***Simply ingesting the plant material, as suggested by Arntzen et al., does not confer immunity*** at least in the sense that there is a protective response.

There is good reason for Arntzen's omission of data showing immune response to HBsAg by ingesting food material containing it, since prior to the present invention, in fact, there was little if any immune response whatsoever to HBsAg in orally ingested tomato juice or any other plant expressing HBsAg. See the enclosed Rule 132 Declaration of Dr. Thanavala. The response, if any, is clearly insufficient for that purpose.

Reference to the examples in the present specification clearly illustrates that priming of the subject of the immunization is required by either pre-vaccination or the use of an effective adjuvant. Arntzen et al. suggests neither. Arntzen et al. doesn't suggest an adjuvant for any purpose whatsoever and certainly does not suggest a combination with an adjuvant that permits the obtaining of a high immune response to orally administered HBsAg as required by the present claims.

Arntzen's suggestion of simple ingestion of plant material expressing HBsAg does not give a sufficient immune response to be considered protective. Arntzen discloses or suggests no way in which a high immune response could be orally obtained. ***In any case there is certainly no suggestion of the enhanced immune response to HBsAg in orally administered plant material as provided by the method presently claimed.***

The Examiner states that Koprowski "teaches methods of making a transgenic plant containing a viral antigen which is fed to an animal or human to elicit an immune response." The Examiner's statement is inaccurate. **Koprowski at al. does not teach or suggest any method for making a transgenic plant** but teaches a microorganism expressing a bioactive compound, e.g. an immunogenic rabies polypeptide. The microorganism may then be used to infect a plant as a parasite but does not alter the genetic character or expression of the plant.

Kaprowski et al. suggest that their method has wide application, e.g. for treatment of viral infections, bacterial infections, fungal infections, protozoan infections, diabetes, immune disorders, cancer and heart disease. Kaprowski et al. more specifically suggest that their method could be used for mucosal pathogens, e.g. rabies, respiratory syncytial virus, cholera. typhoid fever, herpes simplex types I and II, tuberculosis, pathogenic pneumococci, human immunodeficiency virus-1 (HIV-1) and human immunodeficiency virus-2 (HIV-2).

The only specific example given is for rabies. There is no enablement for the other suggested applications. If the disclosure actually enabled everything suggested, oral vaccines effective against Aids, cancer, and herpes, among many others, would be made available simply by following the teachings of the Kaprowski et al patent. It is well known that this is not the case.

Kaprowski et al. certainly does not enable or even reasonably suggest application for orally raising an immune response to hepatitis B surface antigen. The suggestion that

an adjuvant be used is a gratuitous statement applied across the entire non-enabled spectrum of the Kaprowski et al. disclosure. There is no suggestion of any specific adjuvant that would have such an effect for purposes of enablement and in fact there is no suggestion that any adjuvant would have any effect whatsoever upon oral immune response to hepatitis B surface antigen.

Stites et al. adds nothing to cure the inadequate teachings and suggestions of Arntzen et al. and Kaprowski et al. Stites does not suggest anything whatsoever concerning hepatitis B and certainly suggests nothing suggesting that HBsAg would **orally** raise a highly effective immune response in the presence of a suitable adjuvant as presently claimed. Adjuvants "enhance" immune response. Arntzen does not teach any method showing any immune response to be enhanced and especially not with respect to HBsAg.

The necessity for the submission of the accompanying declaration to support arguments already made became clear only upon receipt of the last official action. The last official action made it clear that the technical arguments previously submitted by the attorney for the applicants would not be accepted by the Examiner in the absence of additional support.

No new issues are raised since the declaration and arguments currently presented merely support positions previously taken by the Applicants.

In view of the foregoing remarks and declaration, it is courteously requested that all rejections be withdrawn and all claims be allowed.

Respectfully submitted,

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